

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 October 2008 (30.10.2008)

PCT

(10) International Publication Number
WO 2008/131197 A1

(51) International Patent Classification:

A61L 27/26 (2006.01) C08L 67/04 (2006.01)
A61L 27/50 (2006.01)

(21) International Application Number:

PCT/US2008/060783

(22) International Filing Date: 18 April 2008 (18.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/912,827 19 April 2007 (19.04.2007) US

(71) Applicant: SMITH & NEPHEW, INC. [US/US]; 150
Minuteman Road, Andover, MA 01810 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BROWN, Malcolm
[GB/GB]; 89 Wrenbeck Drive, Otley, Yorkshire (GB).
HALL, Michael [GB/GB]; 54 Lancaster Road, Linthorpe,
Middlesbrough (GB). MONTES DE OCA BALDERAS,
Horacio [MX/GB]; 40 The Green, York YO26 5LR
(GB). ROSE, John [GB/US]; 947 Hardwood View Cove,
Collierville, TN 38116 (US).

(74) Agents: HAINER, JR., Norman, F. et al.; 150 Minute-
man Road, Andover, MA 01810 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE,
EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID,
IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC,
LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN,
MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV,
SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,
NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(54) Title: MULTI-MODAL SHAPE MEMORY POLYMERS

(57) Abstract: The present disclosure relates to a multi-modal shape memory polymer material comprising a blend of at least one polymer component having a first molecular weight and at least a second polymer component having a second molecular weight that is less than the first component.

WO 2008/131197 A1

MULTI-MODAL SHAPE MEMORY POLYMERS***Cross-Reference to Related Applications***

[0001] This application is a PCT International Application of United States Patent
5 Application No. 60/912,827 filed on April 19, 2007, the disclosure of which is incorporated
herein by reference in its entirety.

Background***1. Field of the Invention***

[0002] This present disclosure relates generally to shape memory polymers and, more
10 particularly, multi-modal shape memory polymers.

2. Related Art

[0003] Amorphous orientated shape memory polymers containing single molecular
weight distributions are known to relax and form fixation devices when placed into a bone
cavity. Upon observation, these shape memory polymer materials relax and try to flow into
15 the small pores of bone. Polymers used for current shape memory applications have
molecular weight distributions of polydispersity in the range of between about 2 to about 4.
These types of ranges may limit the ability of the polymer to penetrate into the bone, the
mechanical properties of the polymer itself, or in the case where the polymer is resorbable,
the degradation time of the polymers.

20 ***Summary***

[0004] In an aspect, the present disclosure relates to a multi-modal shape memory
polymer material comprising a blend of at least one polymer component having a first
molecular weight and at least a second polymer component having a second molecular weight
that is less than the first component. In an embodiment, the polymer material is bi-modal. In
25 another embodiment, the first molecular weight has an M_n in excess of about 30,000 Daltons

and the second molecular weight has an M_n of up to about 30,000 Daltons. In yet another embodiment, the first molecular weight has an M_n of between about 50,000 and about 1,000,000 Daltons and the second molecular weight has an M_n of between about 2,000 and about 30,000 Daltons. In a further embodiment, the at least one polymer component
5 comprises about 80% of the polymer blend and the second polymer component comprises about 20% of the polymer blend.

[0005] In an embodiment, the at least one polymer component and the second polymer component are both resorbable. In another embodiment, the at least one polymer component and the second polymer component are both non-resorbable. In yet another embodiment, one
10 of the at least one polymer component and the second polymer component is resorbable and one of the at least one polymer component and the second polymer component is non-resorbable. In a further embodiment, both of the components are miscible. In yet a further embodiment, the material includes a filler selected from a group consisting essentially of hydroxyapatite, calcium carbonate, and tricalcium phosphate.

15 [0006] In an embodiment, the material includes a porogen selected from a group consisting essentially of sodium chloride, lithium bromide, lithium iodide, calcium chloride, sodium iodide, magnesium sulphate, and calcium sulphate. In another embodiment, at least one or both of the at least one polymer component and the second polymer component includes a polyester selected from a group including P(L)LA, poly (D) lactic acid (P(D)LA),
20 poly (DL) lactic acid (P(DL)LA), poly(L-co-DL) lactic acid (P(LDL)LA), poly (L) lactic acid - co-glycolide (P(L)LGA)), poly (DL) lactic acid - co-glycolide (P(DL)LGA)), poly (D) lactic acid - co-glycolide (P(D)LGA)), polycaprolactone (PCL), PGA, and combinations thereof.

[0007] In yet another embodiment, at least one or both of the at least one polymer
25 component and the second polymer component includes a polyacrylate. In a further

embodiment, at least one or both of the at least one polymer component and the second polymer component includes a polymethyl methacrylate polymer or copolymer thereof. In yet a further embodiment, at least one or both of the at least one polymer component and the second polymer component includes a polybutyl methacrylate polymer or copolymer thereof. In an embodiment, at least one or both of the at least one polymer component and the second polymer component includes a polybutyl methacrylate-co-polymethyl methacrylate copolymer. In another embodiment, at least one or both of the at least one polymer component and the second polymer component includes a polystyrene copolymer.

[0008] In another aspect, the present disclosure relates to an article comprising a multi-modal shape memory polymer material comprising a blend of at least one polymer component having a first molecular weight and at least a second polymer component having a second molecular weight that is less than the first component. The article is selected from a group consisting essentially of rods, pins, nails, screws, plates, anchors, and wedges.

[0009] In a further aspect, the present disclosure relates to the use of the article as a fixation device suitable for implantation into bone wherein upon implanting the article into bone and providing the article with energy, the material flows into pores of the bone thereby enhancing fixation of the article to bone.

[0010] In yet a further aspect, the present disclosure relates to an article comprising a multi-modal shape memory polymer material comprising a blend of at least one polymer component having a first molecular weight and at least a second polymer component having a second molecular weight that is less than the first component, wherein upon implanting the article into bone and providing the article with energy, the material flows into pores of the bone thereby enhancing fixation of the article to bone.

[0011] Further features, aspects, and advantages of the present disclosure, as well as the structure and operation of various embodiments of the present disclosure, are described in detail below with reference to the accompanying drawings.

Brief Description of the Drawings

5 [0012] The accompanying drawings, which are incorporated in and form a part of the specification, illustrate the embodiments of the present disclosure and together with the description, serve to explain the principles of the disclosure. In the drawings:

[0013] Fig. 1 is an overlaid chromatograph showing the molecular weight profile distribution of a monomodal polymer material and the multi-modal polymer material of the
10 present disclosure.

[0014] Fig. 2 is a chromatograph showing the molecular weight profile distribution of the multi-modal polymer material of the present disclosure.

Detailed Description of the Embodiments

[0015] The following description of the preferred embodiment(s) is merely
15 exemplary in nature and is in no way intended to limit the disclosure, its application, or uses.

[0016] The present disclosure relates to a multi-modal shape memory polymer material comprising a blend of at least one polymer component having a first molecular weight and at least a second polymer component having a second molecular weight that is less than
20 the first component.

[0017] The first polymer component represents about 80% of the polymer blend and includes a high molecular weight having an M_n in excess of about 30,000 Daltons, and in some embodiments, between about 50,000 and about 1,000,000 Daltons. The second component represents about 20% of the polymer blend and includes a low molecular weight
25 having an M_n of up to about 30,000 Daltons, and in some embodiments, between about 2,000

and about 30,000 Daltons. The high molecular weight of the first component provides the blend with the necessary mechanical strength and the low molecular weight of the second component provides the blend with the necessary flow characteristics and therefore the necessary amount of integration of the blend into bone, as will be further described below.

5 [0018] For the purposes of this disclosure, both the first and second polymer components include a polylactide based shape memory polymer. However, the polymer material may include a resorbable and/or non-resorbable polymer material having shape-memory qualities and which is selected from a group that includes an amorphous polymer, a semi-crystalline polymer, and combinations thereof.

10 [0019] Specific polymers that may be used include polyacrylic/polyacrylate, polymethyl methacrylate (PMMA), polyethyl methacrylate (PEMA), polybutylacrylate, polybutylmethacrylate, polystyrene, poly-alpha-hydroxy acids, polycaprolactones, polydioxanones, polyesters, polyglycolic acid, polyglycols, polylactides, polyorthoesters, polyphosphates, polyoxaesters, polyphosphoesters, polyphosphonates, polysaccharides,
15 polytyrosine carbonates, polyurethanes, and copolymers or polymer blends thereof. Also, the polymer components may be miscible and capable of forming a substantially uniform blend. Polyesters that may be used include P(L)LA, poly (D) lactic acid (P(D)LA), poly (DL) lactic acid (P(DL)LA), poly(L-co-DL) lactic acid (P(DDL)LA), poly (L) lactic acid - co-glycolide (P(L)LGA)), poly (DL) lactic acid - co-glycolide (P(DL)LGA)),poly (D) lactic
20 acid - co-glycolide (P(D)LGA)), polycaprolactone (PCL), PGA, and combinations thereof.

 [0020] Generally, polymers that display shape memory qualities show a large change in modulus of elasticity at the glass transition temperature (T_g). The shape-memory function can be achieved by taking advantage of this characteristic. Namely, the mixture of the first and second polymer components is processed, via processes known to one of skill in the art,
25 to make an article having a definite shape (the original shape). The article is then processed

to give the article a secondary shape and to provide the article with shape memory qualities. The process may process include, without limitation, die drawing, zone drawing, hydrostatic extrusion, compression flow molding, thermoforming, rolling, and roll drawing. The article is then softened by providing the article with energy and heating to a temperature (T_f) higher than the T_g of the polymer, but lower than the melting temperature (T_m) thereof so as to deform the article back to its original shape.

[0021] The article may include fixation devices, such as, without limitation, rods, pins, intramedullary nails, bone screws, locking screws, plates, anchors, staples, and wedges, for use in the repair of bone and soft tissue. In addition, the article may include a sleeve of polymer material, including a central channel, which allows the sleeve to be placed on a fixation device, such as the fixation devices listed above, for subsequent use in fixating the fixation device to bone, as is described in PCT International Application No. PCT/US08/56828, the disclosure of which is incorporated herein by reference in its entirety.

[0022] Examples of adding energy to the polymer material include electrical and thermal energy sources, the use of force, or mechanical energy, and/or a solvent. The thermal energy source may include a heated liquid, such as water or saline. It is also within the scope of this disclosure that once the macroscopic body is placed in the bone, body heat would be transferred from blood and tissue, via thermal conduction, to provide the energy necessary to deform the shape memory polymer material. In this instance, body temperature would be used as the thermal energy source. Examples of electrical energy sources include heat generating devices such as a cauterizing device or insulated conductor, as more fully described in the '828 application, or a heating probe, as more fully described in PCT Application No. PCT/US2008/056836, the disclosure of which is incorporated herein by reference in its entirety.

[0023] Any suitable force that can be applied either preoperatively or intra-operatively can be used. One example includes the use of ultra sonic devices, which can relax the polymer material with minimal heat generation. Solvents that could be used include organic-based solvents and aqueous-based solvents, including body fluids. Care should be taken that the selected solvent is not contra indicated for the patient, particularly when the solvent is used intra-operatively. The choice of solvents will also be selected based upon the material to be relaxed. Examples of solvents that can be used to relax the polymer material include alcohols, glycols, glycol ethers, oils, fatty acids, acetates, acetylenes, ketones, aromatic hydrocarbon solvents, and chlorinated solvents.

[0024] The article may include a composite or matrix having reinforcing material or phases such as glass fibers, carbon fibers, polymeric fibers, ceramic fibers, ceramic particulates, rods, platelets, and fillers. The fillers may include osteoconductive materials and/or biological actives such as, without limitation, hydroxyapatite, calcium carbonate, and tricalcium phosphate. Other reinforcing material or phases known to one of ordinary skill in the art may also be used. In addition, the polymeric material may be made porous via the use of porogens. The porogens include, without limitation, sodium chloride, lithium bromide, lithium iodide, calcium chloride, sodium iodide, magnesium sulphate, and calcium sulphate. Porosity may allow infiltration by cells from surrounding tissues, thereby enhancing the integration of the material to the tissue.

[0025] Also, one or more active agents may be incorporated into the material. Suitable active agents include bone morphogenic proteins, antibiotics, anti-inflammatories, angiogenic factors, osteogenic factors, monobutyrin, thrombin, modified proteins, platelet rich plasma/solution, platelet poor plasma/solution, bone marrow aspirate, and any cells sourced from flora or fauna, such as living cells, preserved cells, dormant cells, and dead cells. It will be appreciated that other bioactive agents known to one of ordinary skill in the

art may also be used. Preferably, the active agent is incorporated into the polymeric shape memory material, to be released during the relaxation or degradation of the polymer material. Advantageously, the incorporation of an active agent can act to combat infection at the site of implantation and/or to promote new tissue growth.

5

EXAMPLE

[0026] A bimodal polymer blend, as described above, was prepared by compounding a mixture containing 35%w/w CaCO_3 , 6.5%w/w Poly(DL-Lactide) (PDLA) (molecular weight, $M_n = 13900$, $M_w = 20500$) and 58.5%w/w Poly(L-co-DL-Lactide) 70:30 (PLDLA) (molecular weight, $M_n = 354700$, $M_w = 854500$) using a twin screw extruder. The resulting material was moulded to produce a 30 mm diameter rod suitable for die drawing. The rod was drawn through a 15mm die at 75 °C at a rate of 20 mm/minute to produce a rod with a diameter of about 15 mm. The rod included shape memory qualities. The resulting rod was machined to produce plugs of 25 mm in length and 13 mm in diameter. Each plug also included an 8 mm diameter central opening. A stainless steel sleeve having a 4 mm diameter central opening was then press fitted into the central opening of each plug. The sleeve had a length of 25 mm and a diameter of 13 mm.

[0027] A monomodal polymer blend, to be used for control purposes, was prepared by compounding a mixture containing 35% w/w CaCO_3 , 65 % w/w Poly(L-co-DL-Lactide) 70:30 (PLDLA) (molecular weight, $M_n = 354700$, $M_w = 854500$) using a twin screw extruder. The resulting material was molded to produce a 30 mm diameter rod suitable for die drawing. The rod was drawn through a 15 mm die at 75°C at a rate of 20 mm/minute to produce a rod with a diameter of approximately 15 mm. The rod included shape memory qualities. Each plug also included an 8 mm diameter central opening. A stainless steel sleeve having a 4 mm diameter central opening was then press fitted into the central opening of each plug. The sleeve had a length of 25 mm and a diameter of 13 mm.

[0028] The molecular weight of both the monomodal and the bimodal polymer blends was determined using gel permeation chromatography (GPC). Table 1 provides the molecular weights of the monomodal and bimodal polymer plugs.

5

Table 1

Material	Molecular weight (Mn)	Molecular weight (Mw)	Polydispersity (Mw/Mn)
Monmodal	97200	244700	2.6
Bimodal	101200	426700	4.2

[0029] Additionally, Figs. 1 and 2 show the molecular weight profile distributions of the monmodal and the bimodal polymer plugs. Specifically, Fig. 1 is an overlaid chromatograph showing graphs 1,2 for both the monomodal polymer plug and the bimodal polymer plug, respectively, and Fig. 2 is a chromatograph showing only the graph 2 for the bimodal polymer plug. The first peak 2a represents the high molecular weight PLLA-co-DL material and the second peak 2b represents the low molecular weight PDLA material.

[0030] Samples of the monomodal and the bimodal plugs, described above, were placed into 14 mm diameter sawbone cavities. Each plug was heated for 15 min at 175°C using a 4 mm diameter heating probe. In order to heat the plugs, the probe was inserted into the central opening of the stainless steel rods. The plugs were then allowed to cool after which the fixation force was measured using the following procedure:

[0031] Each sample of sawbone was placed on a cylindrical support on an Instron 5566 test machine. A rigid metal probe of 8 mm diameter, connected rigidly to a 10kN load cell, was pressed against the one end of each of the plugs at 2 mm/min. The maximum force to push out the plug in each case was recorded and is shown in Table 2 below.

Table 2

Bimodal plug	Push out force (N)
1	2148
2	2265
3	2880
Mean	2431 (+/- 393)
Monomodal plug	
	375
	460
Mean	417 (+/- 43)

[0032] Hence it can be concluded that a multi-modal polymer composition having shape memory qualities contains substantially enhanced mechanical properties compared to a monomodal shape memory polymer composition. It is believed that the enhanced mechanical properties are due to the combination of the high strength high molecular weight polymer and the flow characteristics of the low molecular weight polymer. Specifically, due to the miscibility of the polymer components, it is believed that the lower molecular weight polymer component plasticizes the higher molecular weight component. This aids flow of the multi-modal material into pores of the bone, and hence, fixation of the plug to the bone, thereby providing the plug with enhanced mechanical properties.

[0033] For the purposes of this disclosure, a multi-modal polymer composition is a polymer composition having more than one molecular weight distribution. The multi-modal composition used in this disclosure has two molecular weight distributions (bimodal), however, polymer compositions having more than two molecular weight distributions are also within the scope of this disclosure. In addition, although for the purposes of this disclosure the low molecular weight component is present at about 20% and the high molecular weight component is present at about 80%, the components may be present in any suitable proportions to give the desired increase in strength and flowability. Furthermore, the polymer blend of the present disclosure may be present as a homopolymer blend or as a co-polymer blend.

[0034] In view of the foregoing, it will be seen that the several advantages of the disclosure are achieved and attained.

[0035] The embodiments were chosen and described in order to best explain the principles of the disclosure and its practical application to thereby enable others skilled in the art to best utilize the disclosure in various embodiments and with various modifications as are suited to the particular use contemplated.

[0036] As various modifications could be made in the constructions and methods herein described and illustrated without departing from the scope of the disclosure, it is intended that all matter contained in the foregoing description or shown in the accompanying drawings shall be interpreted as illustrative rather than limiting. Thus, the breadth and scope of the present disclosure should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims appended hereto and their equivalents.

What is Claimed Is:

1. A multi-modal shape memory polymer material comprising a blend of at least one polymer component having a first molecular weight and at least a second polymer component having a second molecular weight that is less than the first component.
- 5 2. The multi-modal polymer material of claim 1 wherein the material is bimodal.
3. The multi-modal polymer material of any of claims 1 or 2 wherein the first molecular weight has an M_n in excess of about 30,000 Daltons and the second molecular weight has an M_n of up to about 30,000 Daltons.
4. The multi-modal polymer material of claim 3 wherein the first molecular weight (M_n)
10 is between about 50,000 and about 1,000,000 Daltons and the second molecular weight (M_n) is between about 2,000 and about 30,000 Daltons.
5. The multi-modal polymer material according to any of claims 1 to 4 wherein the at least one polymer component comprises about 80% of the polymer blend and the second polymer component comprises about 20% of the polymer blend.
- 15 6. An article comprising the material of claim 1 wherein the article is selected from a group consisting essentially of rods, pins, nails, screws, plates, anchors, and wedges.
7. The use of the article of claim 6 as a fixation device suitable for implantation into bone wherein upon implanting the article into bone and providing the article with energy, the material flows into pores of the bone thereby enhancing fixation of the
20 article to bone.
8. An article comprising the material of claim 1 wherein upon implanting the article into bone and providing the article with energy, the material flows into pores of the bone thereby enhancing fixation of the article to bone.
9. The multi-modal polymer material of claim 1 wherein the at least one polymer
25 component and the second polymer component are both resorbable.

10. The multi-modal polymer material of claim 1 wherein the at least one polymer component and the second polymer component are both non-resorbable.

11. The multi-modal polymer material of claim 1 wherein one of the at least one polymer component and the second polymer component is resorbable and one of the at least one polymer component and the second polymer component is non-resorbable.

12. The multi-modal polymer material of claim 1 wherein the both of the components are miscible.

13. The multi-modal polymer material of claim 1 wherein the material includes a filler selected from a group consisting essentially of hydroxyapatite, calcium carbonate, and tricalcium phosphate.

14. The multi-modal polymer material of claim 1 wherein the material includes a porogen selected from a group consisting essentially of sodium chloride, lithium bromide, lithium iodide, calcium chloride, sodium iodide, magnesium sulphate, and calcium sulphate.

15. The multi-modal polymer material of claim 1 wherein at least one or both of the at least one polymer component and the second polymer component includes a polyester selected from a group including P(L)LA, poly (D) lactic acid (P(D)LA), poly (DL) lactic acid (P(DL)LA), poly(L-co-DL) lactic acid (P(DDL)LA), poly (L) lactic acid - co-glycolide (P(L)LGA)), poly (DL) lactic acid - co-glycolide (P(DL)LGA)), poly (D) lactic acid - co-glycolide (P(D)LGA)), polycaprolactone (PCL), PGA, and combinations thereof.

16. The multi-modal polymer material of claim 1 wherein at least one or both of the at least one polymer component and the second polymer component includes a polyacrylate.

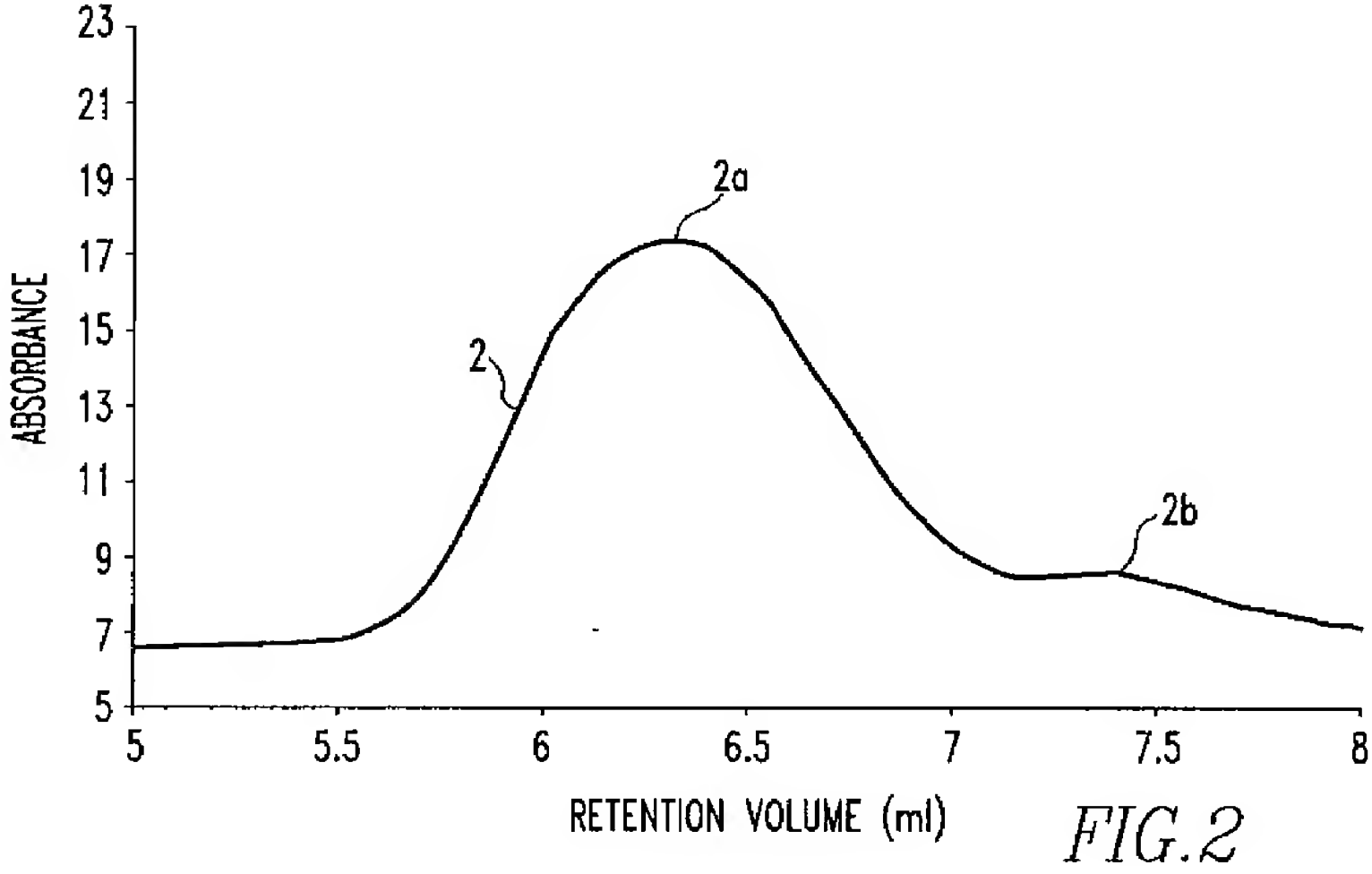
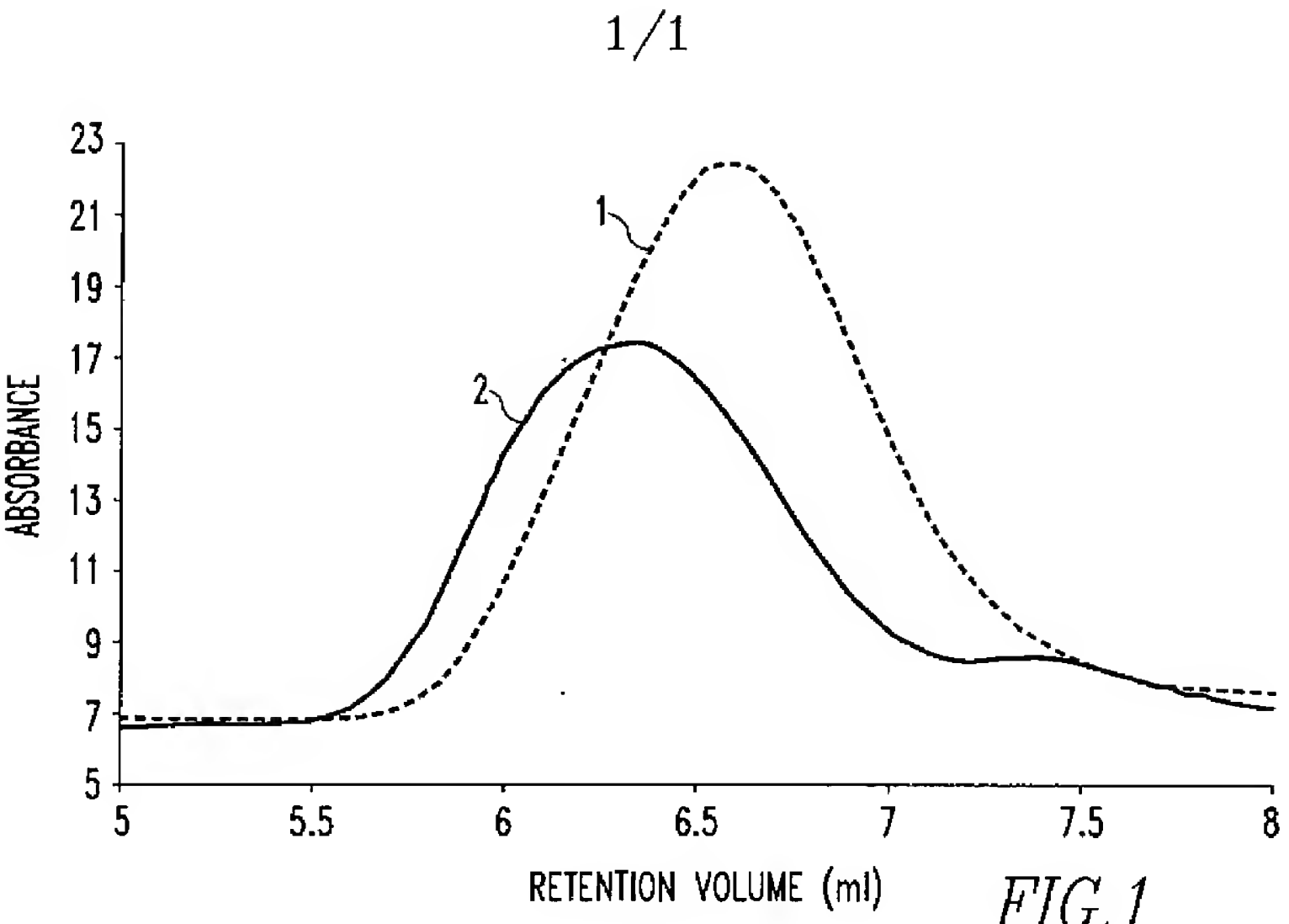
17. The multi-modal polymer material of claim 1 wherein at least one or both of the at least one polymer component and the second polymer component includes a

polymethyl methacrylate polymer or copolymer thereof.

18. The multi-modal polymer material of claim 1 wherein at least one or both of the at least one polymer component and the second polymer component includes a polybutyl methacrylate polymer or copolymer thereof.

5 19. The multi-modal polymer material of claim 1 wherein at least one or both of the at least one polymer component and the second polymer component includes a polybutyl methacrylate-co-polymethyl methacrylate copolymer.

20. The multi-modal polymer material of claim 1 wherein at least one or both of the at least one polymer component and the second polymer component includes a
10 polystyrene copolymer.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/060783

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L27/26 A61L27/50 C08L67/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61L C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/020430 A (SMITH & NEPHEW [GB]; BROWN MALCOLM [GB]) 22 February 2007 (2007-02-22) page 2, line 14 - page 3, line 4 page 4, line 21 - page 5, line 3 page 5, line 24 - page 6, line 19 -----	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

11 July 2008

Date of mailing of the international search report

23/07/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lohner, Pierre

Information on patent family members

PCT/US2008/060783

Patent document
cited in search report.

Publication date

Patent family member(s)

Publication date

WO 2007020430	A	22-02-2007	AU	2006281246 A1	22-02-2007
			CA	2619552 A1	22-02-2007
			EP	1926506 A2	04-06-2008